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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/040,570	11/01/2001	Martyn Frank Burslem	PCS10895ANIS	2725

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EXAMINER	
BERTOGLIO, VALARIE E	

ART UNIT	PAPER NUMBER
1632	12

DATE MAILED: 03/27/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/040,570	BURSLEM ET AL.	
	Examiner	Art Unit	
	Valarie Bertoglio	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02/24/2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-20* is/are pending in the application.

4a) Of the above claim(s) *8-20* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *01 November 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

Election/Restrictions

Applicant's election of Group I, claims 1-3 in paper No. 11, with traverse is acknowledged. The traversal is on the ground(s) that a search of the genetically modified animals of Group I would provide useful information on the cells of Group II, claims 4-7. This is found partially persuasive in that the cells of Group II, as they relate to cells comprised by the animals of Group I. As such, Groups I and II will be rejoined, however, claims 4-7 will be examined only as they relate to cells in vivo and are comprised by the animals of Group I.

Claims 4-7 as they relate to cells in vitro and claims 8-20 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Claims 1-7 are currently under consideration.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claim 6 is rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. Claim 6 encompasses transgenic human cells in vivo, which is a cell comprised by a transgenic human. Transgenic humans are non-statutory subject matter.

Priority

Applicant claims priority to US provisional application 60/293411, filed 05/27/2001. However, USPTO records indicate the filing date for US provisional application 60/293,411 is 05/24/2001. The filing date listed in the Oath and in the first line of the specification are both 05/27/2001. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-7 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116).

Claims encompass any non-human mammal comprising a genetic modification that functionally disrupts PDE11A (claims 1-3) and cells derived from said mammals (claims 4-7). Claims encompass not only physical disruption of the PDE11A gene, but also disruption of gene product function (page 17, lines 20-33). For example, a transgenic animal comprising a randomly inserted transgene encoding PDE11A antisense is encompassed by the claims. Claims also encompass random chemical or irradiation mutagenesis. However, the specification only describes a mouse generated by targeted gene insertion and disruption of the PDE11A gene. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of making it. Therefore, the specification fails to provide adequate written description of a genetically modified non-human mammal other than a mouse generated by targeted gene insertion.

Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

Claims 1-7 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a mouse comprising a homozygous targeted gene disruption of the PDE11A gene wherein the mouse exhibits reduced spermatogenesis (page 42, lines 11-18) or increased capacitation (page 43, lines 33-34) and for cells comprised by said mouse, does not reasonably provide enablement for any species of genetically modified non-human mammal comprising any modification resulting in a functionally disrupted PDE11A gene wherein the mammal is any non-mouse species and wherein the mammal has any phenotype or for cells comprised by any of said non-mouse species. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Claims are directed to a genetically modified, non-human mammal wherein the modification results in a functionally disrupted PDE11A gene (claim 1) wherein the mammal is a rodent (claim2) or wherein the mammal is a mouse (claim3). Claims are also directed to cells comprised by a genetically modified mammal wherein the modification results in a functionally disrupted PDE11A gene (claim 4) wherein the cell is an ES cell (claim 5) or a human cell (claim 6) or a murine cell (claim 7).

1) The specification is not enabling for the disrupting PDE11A function using any means other than targeted gene insertion. The specification describes using antisense gene technology or using chemical or irradiation mutagenesis to disrupt PDE11A function (page 17, lines 20-33). However, the specification does not teach how to use either of these techniques.

The state of the art of antisense technology at the time of filing was that the design and use of anti-sense nucleic acid sequences was a highly unpredictable art that required extensive experimentation in the elaboration of appropriate nucleic acid constructs that when introduced into a host cell would cause inhibition of expression of a particular gene or gene product.

Rossiter et al. (1989, Advances in Applied Biotechnology Series, pp. 57-69) found that anti-sense sequences derived from different regions of the HPRT gene have varying levels of effectiveness in reducing HPRT expression (pages 60-61). Furthermore, complete inhibition of HPRT expression was not obtained in vivo (page 67, paragraphs 2-3). It is well known in the art that identification of binding sites in a given RNA species resulting in inhibition of gene expression is an unpredictable art. Hoke (1996, USPN 5,585,479) states that "there are no rational explanations or rules that would predict active sequences." There are a number of variables that can affect the effectiveness of various antisense RNA molecules. For example, some anti-sense species could form inactivating secondary structures or bind to and inhibit other RNA molecules encoding gene products other than the targeted gene product.

While the state of the art at the time of filing would enable one of skill to mutagenize the PDE11A gene using chemicals or radiation, one would not know whether any mutation recovered functionally disrupts PDE11A according to the current invention. Because the claim does not state a phenotype, and the phenotype of such an animal cannot be predicted, one of skill in the art would not know whether any nucleotide change in the PDE11A alters the phenotype of the animal such that the claimed invention had been attained. As such, one would not know how to use a mammal comprising any chemically induced mutation that disrupts any function of PDE11A as broadly claimed.

Therefore, due to the lack of guidance in the specification and the unpredictability as set forth in the art, the specification fails to enable making and/or using genetically modified non-human mammals wherein PDE11A function is disrupted as a result of an anti-sense polynucleotide, chemical or radiation mutagenesis, or any other technique other than targeted-gene insertion. Claims 4,5 and 7 encompass cells from non-human transgenic mammals having a disruption in the PDE11A gene. Without the guidance necessary to generate the mammals,

one is not enabled for the cells comprised by animal. Claim 6 can be interpreted as implying a genetically modified human as the claim relates to genetically modified human cells in vivo. However, no genetically modified human has been made. Without being enabling for the genetically modified human, the specification fails to be enabling for the cells within the human.

2) The specification does not provide adequate guidance for one of skill in the art to make and use non-human transgenic mammals having a gene insertion disruption in the PDE11A gene in any species other than mouse.

The methods of gene targeting such as employed in the instant invention require embryonic stem cells. The state of the art at the time of filing was that ES cell technology was not available for targeted mutagenesis in generating transgenic animals in any species other than mouse. Other methods of producing mammals using gene targeting were highly unpredictable. Mullins (1996, J. Clin. Invest., Vol. 98, pages S37-S40) taught that non-mouse ES cells capable of providing germline chimeras were not available (page S38, column 1, first paragraph). Campbell and Wilmut (1997, Theriogenology, vol. 47, pp, 63-72) acknowledge reports of ES-like cells in a number of species, but emphasize that as yet there are no reports of any cells lines that contribute to the germ line in any species other than mouse (page 65). Other potential methods of generating transgenic embryos using homologous recombination had not been fully developed at the time the invention was made (McCreath, 2000, Nature, Vol. 405, pages 1066-1069; Kent-First, 2000, Nature Biotechnology, Vol. 18, pages 928-929; Dinnyes, 2002, Cloning and Stem Cells, Vol. 4, pages 81-90). The first report gene targeting in a lamb produced by somatic cell nuclear transfer of nuclei from using fetal fibroblasts (McCreath, 2000) reported abnormal transgene expression/function. The first knockout lamb using this technique was not reported until after the effective filing date of the instant invention and also met great difficulty (Denning, 2001, Nature Biotechnology, Vol. 19, pages 559-562). Furthermore, cloned

fetuses, irrespective of whether they are genetically modified, are often abnormal and nonviable with no consistent pattern of abnormality to indicate the cause of the defects (Dinnyes, page 87, column 1, 3rd full paragraph; McCreath, paragraph bridging pages 1067 and 1068). It would be difficult to determine whether the phenotype resulting in a genetically modified animal generated by somatic cell nuclear transfer was a result of the genetic modification or an artifact of the nuclear transfer technique. Thus, at the time of filing, the phenotype of transgenic knockout mice was unpredictable and knockout animals could not be prepared for any species other than mouse.

The teachings in the specification are limited to gene targeting in mouse ES cells followed by injection of the ES cells comprising a targeted disruption in the PDE11A gene into a blastocyst to generate transgenic mice (page 34, lines 7-13). No teachings or guidance are offered in regard to how one would have prepared any other species of mammal with a desired phenotype using targeted mutagenesis. Without such guidance, it would require undue experimentation for one of skill in the art at the time of filing to make any transgenic, non-human animal, other than mouse, with a disruption in the PDE11A gene. Claims 4-7 encompass cells from genetically modified non-human mammals (4,5 and 7) or human (claim 6) having a disruption in the PDE11A gene. Without the guidance necessary to generate the mammals or human, one is not enabled for the cells comprised by the mammals.

3) Applicants fail to enable making and/or using genetically modified, non-human mammal comprising a genetic modification that results in a functionally disrupted PDE11A gene wherein the mammal has any phenotype other than reduced spermatogenesis or increased capacitation as broadly claimed (claims 1-3).

The art at the time of filing also that the phenotype of transgenic knockout mice was unpredictable. Leonard (1995, Immunological Reviews, Vol. 148, pages 98-113) disclosed mice

with a disruption in the g_c gene that was intended to be a model for X-linked severe combined immunodeficiency (XSCID), but display a variety of unexpected traits (abstract). These knockout mice were expected to have thymocytes with decreased proliferation in response to stimulation with antibodies, but the thymocytes proliferated normally (page 105, line 7). Griffiths (1998, Microscopy Research and Technique, Vol. 41, pages 344-358) taught that, despite a known role for the PLP gene based on spontaneous mutations in the gene, the knockout mouse failed to display any of the expected phenotypes (page 350, last paragraph).

Without such guidance as to how to make and use a transgenic PDE11A knockout animal exhibiting any or all possible phenotypes, it would require one of skill in the art at the time the invention was made, undue experimentation to make and/or use the mammals as broadly claimed. Claims 4-7 encompass cells from genetically modified non-human mammals (4,5 and 7) or human (claim 6) having a disruption in the PDE11A gene. Without the guidance necessary to generate the mammals or human, one is not enabled for the cells comprised by the mammals.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1 and 4-7 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1 and 4 are unclear as they use the phrase "functionally disrupt" with the word "gene". It is not clear if the claims are meant to only encompass actual disruption in the PDE11A gene proper or if they also encompass other genetic modifications that affect PDE11A protein

function. The term "function" generally relates to gene products, not genes, as the genes themselves have no active function. Clarification is necessary.

Claims 4-7 fail to distinctly claim the elected invention, which is the cells as they are located in vivo within the mammals of claims 1-3. As such, claims should be limited to cells in vivo.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Valarie Bertoglio whose telephone number is 703-305-5469. The examiner can normally be reached on 7:30-4:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Reynolds can be reached on 703-305-4051. The fax phone numbers for the organization where this application or proceeding is assigned are 703-872-9306 for regular communications and 703-872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-1234.

Valarie Bertoglio
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